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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY/DOCKET NO.
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EXAMINER	
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EXAMINER: THE P. F. F. P.
WILFRED GREENE IS THE EXAMINER
6000 ALEXANDER PARKWAY
BOSTON, MA 02101

ART UNIT	PAPER NUMBER
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1004

DATE MAILED: *Aug 6, 1998*

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

2/23/98

Responsive to communication(s) filed on _____

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 13, 14, 16-18, 21-34 is/are pending in the application.
Of the above, claim(s) 17, 29, 31-34 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) _____ is/are rejected.

Claim(s) _____ is/are objected to.

Claim(s) _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d)

All Some* None of the CERTIFIED copies of the priority documents have been

received

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e)

Attachment(s)

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

SEE OFFICE ACTION ON THE FOLLOWING PAGE

Claims 13-14, 16-18 and 21-34 are pending. Applicants' election of Group I (claims 13, 14, 16-18, 21-30) without traverse is acknowledged, as is the "elected specie". Pursuant to the "election of species", claims 17 and 29 are withdrawn from consideration along with the non-elected claims. Claims 13, 14, 16, 18, 21-28 and 30 are examined in this Office action.

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Applicants should revise the abstract to reflect the subject matter now claimed. In addition, the length of the abstract should be reduced to less than one page.

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It appears that the specification does not recite or define the term "substantially pure". Applicants are requested to point out the location in the text where support for this term

not appear.

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Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not define the term "substantially pure". More often than not, this term is used to describe a mixture which is not pure. It is permissible to use this term if it is defined; otherwise it is subject to broad interpretation.

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The specification is objected to under 35 U.S.C. §112, first paragraph, for failing to provide an enabling disclosure.

Applicants have alleged that "[w]ith A3.5, Ala-boroPro suppressses HIV below detectable levels in a manner similar to the anti-HIV effect of AST at 1 μ M". Applicants have also stated (p. 20) that Ala-boroPro and Pro-boroPro inhibit DP-IV *in vitro*. Applicants are extrapolating, however, to various other embodiments in which non-conservative amino acid substitutions are required. Enzymes are fastidious with respect to the substrates they will recognize; the effects of varying the N-terminal amino

position, and they are both hydrophobic. If the second amino acid (from the "C-terminus") is at all important to enzyme recognition, loss of activity is likely with these embodiments.

Claims 13, 14, 16, 21-28 are rejected under 35 U.S.C. §112, first paragraph, for the reasons set forth in the objection to the specification.

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Claims 13, 14, 16, 21 and 22 are rejected under 35 U.S.C. §102(e) as being anticipated by Bachovchin (USP 4,935,493).

As indicated previously, Bachovchin teaches the following dipeptide:

Pro-boroPro.

(See the formula in col 1, line 50+; also "X" can be prolyl as stated in col 2, line 47).

Applicants have correctly pointed out that in col 7, line 67 it is stated that the both enantiomers of boroPro are present. Applicants have argued that the reference therefore teaches a racemic mixture. Actually it is a mixture of *diasteriomers*, i.e., the following two compounds:

L-Pro-L-boroPro and L-Pro-D-boroPro

Nevertheless, a rejection under §102, rather than §103, is entirely defensible. This is because instant claim 13 is silent as to the disposition of the stereochemistry of the

than glycine. For this embodiment, there would be no fewer than 22 chiral centers. For a compound that has 22 chiral centers, there can be at least 4,194,304 stereoisomers. Accordingly, one of the embodiments encompassed by claim 13 is a mixture of 4,194,304 stereoisomers. Similarly, claim 23 encompasses a mixture of 4,194,304 stereoisomers; the mere fact that so many stereoisomers are present in the same vial does not, in and of itself, preclude the mixture from being 99% pure. Similarly, there is nothing to prevent a mixture of L-Pro-L-boroPro and L-Pro-L-boroPro from being 99% pure.

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Claims 13, 14, and 16 are rejected under 35 U.S.C. §102(a) as being anticipated by Bachovchin (*J. Biol. Chem.* **265**, 3738, 1990).

Bachovchin teaches (e.g., table I, page 3740) several compounds falling within the scope of claim 13.

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Claims 23-25 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (*J. Biol. Chem.* **265**, 3738, 1990).

Bachovchin teaches (e.g., table I, page 3740) several compounds falling within the scope of claim 23. The reference does not employ the phrase "substantially pure

further purification. The presence of impurities, together with the compound of interest, gives rise to a "substantially pure preparation".

The claims are rendered obvious.

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Claims 18, 23-28 and 30 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (USP 4,935,493).

The teachings of the reference were indicated previously. The reference does not employ the phrase "substantially pure preparation". However, the organic chemist of ordinary skill is acutely aware that upon synthesizing a given compound, some impurities are nearly always present prior to further purification. The presence of impurities, together with the compound of interest, gives rise to a "substantially pure preparation". Moreover, the term at issue could be viewed as supergeneric to the term "pharmaceutical formulation", the attainment of which would have been obvious to the pharmaceutical chemist of ordinary skill.

The claims are rendered obvious.

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Claims 13, 14, 16, 18, 21-28 and 30 are rejected under 35 U.S.C. §103 as being unpatentable over Bachovchin (WO 89/03223) or Flentke (*Proc Natl Acad Sci* **88**,

scope of the claimed genus.

The claims are rendered obvious.

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The following pertains to applicants' I.D.S.:

A) The following references were received but were stricken from the IDS:

- 1) Colowick, *Methods in Enzymology* pp. 220-225 (applicants should provide a complete citation, including the volume number and year of publication). [Ref C1].
- 2) Cordes, "Transition States for Hydrolysis of Acetals..." chapter 11 (applicants should provide a complete citation, including the name of the book and year of publication) [ref C2].
- 3) All of the references designated C48 through C119, as well as C28 have been stricken from the IDS. Applicants may provide: (a) a copy of any reference which they would like to have considered or (b) a copy of any Chemical Abstracts citation that is of interest. The citation on the IDS should be of a nature such that an interested party may, at some time after publication of the patent, obtain a copy of the exact reference that was considered by the examiner; moreover, if only the abstract was considered, it should be absolutely clear from the record that the full article itself was never considered.

B) The following references were not received, or were not received in full:

1) Baugh "Proteinases and Tumor Invasion" A copy of a single page (p. 165) was provided, but there is no indication of the reference source. Moreover, none of the other pages have been provided. In addition, the citation should be sufficiently

Applicants should determine the economic impact of the proposed development and make appropriate corrections.

- 2) The two Bodanszky references C5 and C6 were stricken from the IDS. Applicants have provided only a few pages from these books; applicants should provide a copy of the specific pages that they would like to have considered.
- 3) Baily [Ref C12] has been stricken; although a table of contents has been provided, none of pages 1-81 were provided.
- 4) Nicola [Ref C26] has been stricken; although a table of contents has been provided, none of pages 1-257 were provided.
- 5) The Pierce Catalog [Ref C27] has been stricken from the 1449; although a table of contents has been provided, none of the remaining pages of the catalog were provided.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is (703) 308-3213.

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



DAVID LUKTON
PATENT EXAMINER
GROUP 1600